UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 6 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: EPA Reg. No. 8340-13; Endosulfan (Thiodan)●
Caswell No. 420
Accession No. 252043

TO: George LaRocca
Product Manager (15)
Registration Division (TS-767)

THRU: Christine F. Chaisson, Ph.D. C F Chaisson 11/5/84
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: George Z. Ghali, Ph.D. G. Ghali 11/2/1984
Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant: American Hoechst Corporation
Somerville, NJ 08878

11/06/84

Action Requested:

1. Review and evaluation of a dermal sensitization study with Guinea pigs.

2. Evaluation of a proposed emergency treatment for acute intoxication.

3. Evaluation of protocols for acute delayed neurotoxicity, and 13-week feeding studies in rats and mice.

Conclusions and Recommendations:

1. Dermal sensitization in Guinea pigs:
This study has been recently submitted by Makhteshim - Agan (America) Inc., under accession number 252182. In a review by G. Ghali dated October 1984, it was concluded that "under the test conditions, endosulfan did not seem to induce skin sensitization in the test animals". However, since no concurrent or, at least, periodical positive control was included to validate the sensitivity of the test, the study was considered of supplementary nature. The classification of this study may be elevated to Core-minimum upon the receipt and evalution of data on the concurrent or periodical positive control conducted in the same lab for the same species and strain of animals.

2. Proposed emergency treatment:
Based on the information provided by the registrant, the Agency has determined that treatment with diazepam seems to be effective in reducing the severity of the convulsive episodes. However, diazepam should not be regarded as an antidote for cases of intoxication with endosulfan.

3. Protocols evaluation:
The Agency has reviewed protocols for acute delayed neurbtoxicity and 13-week feeding studies in rats and mice. The protocols are considered adequate and conform to the guideline requirements and specifications.

DATA EVALUATION RECORDS

Jung and Weigand (1983). Test for sensitization properties in female Pirbright-White guinea pigs. An unpublished report prepared by Hoechst Ag. Study No. 83.0115 submitted by Makhteshim-AGan (America) Inc. on January, 1984.

Accession Number: 252182

Laboratory: Hoechst Department of Pharmacology and Toxicology, Frankfurt, postfach 800320.

Test Material: Endosulfan technical 97.2% ai, Hoe 002671 OI A097 0003 described as brown flakes.

Protocol:

1. Female Pirbright - White guinea pigs, Hoe: DHPK(SPEL), 8-10 weeks old, weighing 309-379 gm were acclimatized at least 5 days prior to the commencement of the study.

2. According to the authors, about 24 hours before the start of the test the hair on the flank skin of each animal was removed with an electric clipper over an area of about 25 cm^2. The test substance or vehicle was applied to 2.5 x 2.5 cm cllulose patches of a specially manufactured surgical plaster (Baiersdorf AG, Hamburg), which were then fixed in place on the skin. The bodies of the animals were then wrapped round with an elastic polyurethane warp-thread bandage ("Dauerbinde F", manufactured by Lohmann).

Determination of the primary non-irritant concentration:

In order to determine the concentration of the test substance still causing primary skin irritation, 0.5 ml of various concentrations of the test substance were applied in the first preliminary study to the shaved flank skin of Pirbright-White guinea pigs, one animal being used for each concentration level. The substance Hoe 002671 OI ZD97 0003 was tested over an exposure period of 6 hours in the following concentrations:

0.1 % in polyethylene glycol 400
1.0 % in polyethylene glycol 400
10.0 % in polyethylene glycol 400
20.0 % in polyethylene glycol 400
40.0 % in polyethylene glycol 400

Evaluation of the irritant effect took place 24 and 48 hours after application.

Based onthe results of the first preliminary study, which showed that no irritant effects occurred at any of the concentrations tested, a 40% concentration of the substance in polyethylene glycol 400 was tested on 5 Pirbright-White guinea pigs in a second preliminary study in order to determine exactly the highest concentration no longer causing primary irritation. The exposure period was 6 hours. Evaluation took place 24 and 48 hours after application.

Based on the results of this preliminary study, the concentration for use in the main study was indicated as 40 % in polyethylene glycol 400.

Study for testing sensitizing properties:

For the main test 30 Pirbright-White guinea pigs were treated. Over a period of 3 weeks 20 animals were each treated 9 times (3 times per week) epicutaneously with 0.5 ml of a 40 % concentration of Hoe 002671 OI ZD97 0003 in polyethlene glycol 400, which had been shown in the preliminary study to be the highest non-irritant concentration. As a control, 10 other animals were treated with 0.5 ml polyethylene glycol 400 only. After 6 hours exposure the patch was removed and the skin washed with warm water.

After the last application the animals remained without treatment for 16 days. This was followed by two challenge treatments at an interval of 48 hours with 0.5 ml of the 40% dilution of the test material, the highest concentration no longer causing primary irritation. The 10 control animals were also included in the challenge treatments and received 0.5 ml of the 40 % dilution of the test substance also. Evaluation of the skin reaction took place 24 and 48 hours after the two applications.

Signs of primary irritation 24 and 48 hours after application were evaluated as threshold values for significant findings.

*Parts of the methedology were taken directly from the original report.

Results:

In the preliminary study, concentrations of upto and including 40 % of the test material wre tolerated without any signs of skin irritation.

Following the first and the second challenge treatments, there was no occurance of erythema or edema neither int he treatment nor in the control groups.

The treatment did not seem to have any effect on the body weight gain. One animal died on day 24 of the study. Macroscopic autopsy on this animal revealed the following: dark red foci on the lung, stomach lightly filled with air, spleen light in color, lobular markings on the liver, and some kidney areas light in color. However since the autopsy of all animals killed at the end of the study revealed no macroscoic abnormalities, these findigns in the dead animals are not considered treatment-related.

Conclusion:

Under the conditions of this study the test chemical did not induce skin sensitization in guinea pigs. The mean skin sensitization score is zero. However, since no concurrent or periodical positive control data were included in this study, the test sensitivity could not be validated.

Core Classification:

Core-supplementary data. The study might be elevated to Core-minimum upon the receipt and evaluation of data on concurrent or periodical positive control.

DATA EVALUATION RECORDS

Rimpan, MWK (1983) endosulfan Emergency Treatment. Unpublished report dated Nov. 15, 1983 submitted by Hoechst Actiengesellschaft on Dec. 27, 1983.

Accession Number: 252043.

In this report the registrant addressed the issues of emergency treatment and antidote. The report did not include any experimental results, but rather a general discussion for these issues. The registrant stated in this report that:

"Endosulfan technical is classified as a sulfurous acid ester of a cyclic diol. (Materials 5/78. Handbook of Hazardous Substances in Speical Wastes, prepared by the Federal Office of the Environment by order of the Federal Minister of the Interior of the Federal Republic of Germany. Published by: Federal Office of the Environment, Bismarckplatz 1, 1000 Berlin 33, Headed by Offhaus, E., and W. Genest).

It is common knowledge, that for endosulfan - like other chlorinated hydrocarbons - no specific antiodte is known until now, and symptomatic treatment is recommended so far. Therefore the emergency treatement - as attached - does not refer to a specific antidote.

However, Hoechst AG will continue its efforts and investigations in order to find an antidote, which might prove suitable as a therapeutic measure. There are indications that certain substances might be useful in this respect. However, reproducible data are not yet available, and presently we cannot predict when they will be ready."

The registrant suggested the following first aid in addition to some guidance to physicians handling cases of acute intoxication of endosulfan:

First aid

Call a physican.

Protect patient from further contamination. Remove splashed clothing (including underwear) immediately.

Wash moistened skin thoroughly with soap and rinse with running water.

Eyes: Flush out for 10-15 min. with gentle jet of water.

In case of oral intake, induce vomiting (only if patient is conscious): drink glass of water containing 3 teaspoons of salt; where necessary, irritate back of throat with finger.

Ensure that patient has fresh air and remains in lying position. Keep patient warm.

Guide to physician

Endosulfan = sulfite ester of a cyclic diol.

Endosulfan poisoning first exhibits prodromal symptoms in the form of headache, dizziness and disorientation.

Two-3 hours after the initial symptoms, attacks of convulsion and pathological EEG changes are observed.

As a result of acute endosulfan poisoning a mental disorder (chronic brain syndrome) can develop.

Cleanse skin and hairy parts of the body with liberal amounts of polyglycol.

In case of oral intake it is advisable first to carry out gastric gavage and then administer 30 g animal charcoal and 30 g sodium sulphate.

For convulsions:

Administer i.v. diazepam and 10% calcium gluconate. Also apply oxygen and if necessary use a respirator. Otherwise apply symptomatic treatment.

Absolutely contraindicated are epinephrine derivatives.

Discussion and Conclusions:

Endosulfan has a very high acute toxicity to mammals via oral, dermal, and inhalation routes. The major symptoms of acute intoxication are manifested as tremors and convulsions indicating possible involvement of the central nervous system as a possible target site.

Khanna et al. (1979, MRID 05004972) studied the effects of endosulfan on the cat brain. Endosulfan in propylene glycol was administered interveneously at a concentration of 23 mg/kg. The concentration in the lipids of the cat brain 15 minutes and up to six hours after administration was three

times greater in the cerebral cortex and cerebellum tan in the brain stem and spinal cord. The intensity of the convulsions and termors correlated well with the concentration of endosulfan in all areas of the central nervous system.

It should be emphasized also hat endosulfan exists in two isomers designated as I and II. These two isomers may have different modes of action. Gupta (1978, MRID 05003361) found that after repeated oral administration of 5 or 10 mg/kg of endosulfan to rats, the compound was detected in the plasma and different parts of the brain. The amount of endosulfan I in the brain was in proportion to the blood level of the isomer. This was not the case for endosulfan II whose concentration in the brain was much less than expected from the plasma levels. This indicates the difference in the rate of metabolism and elimination of the two isomers.

Treatment with diazepam is known to be effective in reducing the severity of the convulsive episodes especailly those of centrally mediated origin. However this treatment should not be regarded as an antidote. Further studies are deemed necessary to elucidate the mode of action of endusulfan and to develop a more efficacious antidote for emergency treatment of the acute poisoning cases.

References Cited:

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